Drug safety tests and subsequent clinical experience

A P Fletcher MB PhD
Department of Health and Social Security, Finsbury Square House, London EC2A 1PP

Most major new drugs are assessed by the Committee on Safety of Medicines on two occasions before they are permitted to go on the market. The first is the application for a Clinical Trial Certificate and the second is the application for a Product Licence. In this country we work according to the principle that, as far as it is possible, the patient in a clinical trial should be protected from undue hazard just as much as the patient who is prescribed the drug when it is on the market. This is clearly not completely realizable because the state of knowledge at the clinical trial stage will be less complete than at the Product Licence stage.

The assessment of a drug for a Clinical Trial Certificate relies heavily on animal data and, therefore, depends on the validity of the hypothesis that toxicity, or the lack of it, demonstrated in animals is relevant to the situation in man. In general terms, a fair degree of confidence in the hypothesis is probably justifiable, but when specific instances are considered the position is much more doubtful. Because of this it is usual to make decisions that are well on the safe side, so that the appearance of almost any serious animal toxicity may be regarded as sufficient evidence to reject the drug when it comes to considering its use in man. This may not be the correct decision as some toxicity is species-specific and it seems likely that occasionally potential new drugs are rejected unnecessarily.

The present paper deals with 45 major new drugs that have been considered by the Committee on Safety of Medicines during the past eight or nine months. Because of the need to preserve confidentiality, the drugs concerned will not be identified by name but only by type, e.g. psychotropic agent, antihypertensive agent, etc. In making the decision whether to accept or reject these applications, it is of importance to know to what extent, in this series of drugs, toxic effects observed in the animal studies predicted the adverse effects that were observed in the clinical trials. The data from both Clinical Trial Certificate and Product Licence applications have been included. In the case of the former, the clinical data were derived largely

Table 1. Classification of 45 drugs recently assessed by the Committee on Safety of Medicines

	No. of drugs
Antihypertensives	7
CNS agents	6
Nonsteroid anti-inflammatory	4
Bronchodilators	4
Antibiotics	4
Analgesic	3
Cardiac agents	3
Lipid-lowering agents	2
Peripheral vasodilator	2
Cerebral vasodilator	1
Antihistamine	1
Anticancer	1
Antidiabetic	1
Dopaminergic agent	1
Anti peptic ulcer	1
Hormone	1
Antifungal	1
Steroid inhibitor	1
Antiprostatic	1

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from trials done abroad or from volunteer clinical pharmacology studies. The series contained a wide variety of drugs (Table 1), the most common of which were antihypertensive agents and substances active on the central nervous system (CNS).

This paper attempts to answer three questions: (1) to what extent new drug assessment relies upon animal data; (2) what degree of correlation, if any, exists between toxicity in animals and adverse side effects in man; and (3) what reliance can be placed upon animal data as a predictive method.

Reliance of drug assessment on animal data

In the present series of 45 drugs recently assessed by the Committee on Safety of Medicines, the total number of studies reported comprised 1667 animal studies, 124 human volunteer studies and 908 clinical trials. Of the 1667 animal studies, rather more than half were predominantly pharmacological in nature, whilst the remainder were primarily or solely toxicological. The term 'study' is somewhat vague, but for the purposes of this paper it is defined as an experiment or group of experiments reported as a distinct self-sufficient investigation. Thus the effects of a drug on the cardiovascular system of the cat and the dog, if written up and summarized together, would have counted as a single animal study. On the other hand, LD_{50} testing on mouse, rat and rabbit, each at different dosage levels, would be regarded as three animal studies. Reproduction and carcinogenicity testing are regarded as toxicological studies.

The number of animal studies reported varied greatly from one drug to another, the least being 5 in the case of an antifungal agent and the most being 123 in the case of a nonsteroidal anti-inflammatory drug. In this series of drugs there were, therefore, approximately 830 animal toxicology studies and 1032 clinical trials and volunteer studies. As would be expected, the Clinical Trial Certificate applications relied predominantly on animal data whereas the Product Licence applications were mainly reports of human data.

Correlation between toxicity in animals and adverse side effects in man

In this series, every investigation has been checked and each toxic effect in animals or adverse effect in man has been noted. A report was regarded as positive even when an element of doubt existed and was only rejected if reasonable proof seemed to have been offered that the effect was not drug-related. A toxic effect or adverse reaction was recorded as a single event, whether or not it occurred on one or many occasions. Thus hepatotoxicity may have been demonstrated in a 28-day rat study at three dosage levels, in a 6-month rat study at two dosage levels and in a 3-month study at all dosage levels, but this would be recorded as a single toxic event for that drug. Equally, hepatotoxicity at one dosage level in one investigation in one species would also be recorded as a single toxic event. A similar principle was used in recording adverse reactions in clinical trials. This method is open to objections, but simplification was necessary in view of the vast amount of data that was available and the widely varying experimental conditions that were employed.

The results of assessing the data in this way are shown in Figure 1. It will immediately be seen that some effects were only observed in animals and others, because they are not detectable in animals, were exclusive to man. Ataxia and convulsions, which were frequently reported in animal studies, were largely accounted for by agonal signs and symptoms in acute (LD_{50}) toxicity testing. In general, however, effects that were frequent in animals were also frequent in man and conversely effects that were uncommon in animals were uncommon in man. Reproduction abnormalities which are commonly reported in animals are, due to the exclusion of women of childbearing potential, rarely seen in the human. Hepatic and renal toxicity, which are the two most commonly observed effects in animals, are less frequently seen in man but this is probably largely due to lower doses, careful monitoring and shorter duration of treatment. It is of interest that vomiting and gastrointestinal disturbances are approximately equally seen in animals and man, and when individual drugs are looked at in detail the correlation is good. Hypotension and skin rashes were more commonly reported in man than in animals, the former being somewhat alarming in that unanticipated hypotensive episodes

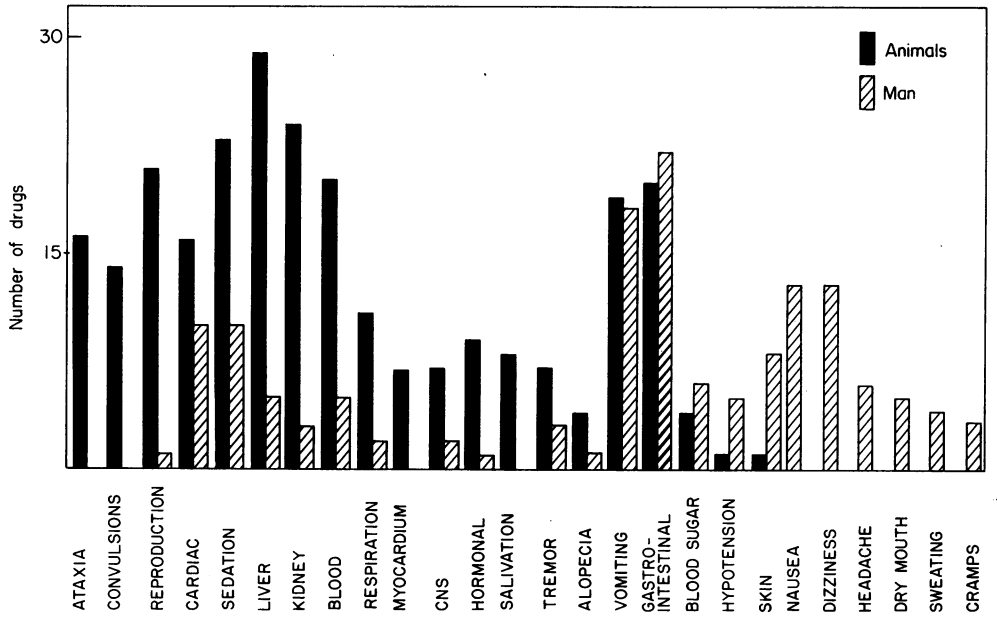

Figure 1. The number of drugs for which the common toxic effects in animals and the adverse side effects in man was reported.

occurred with three drugs that were not hypotensive agents. This potentially serious adverse effect was not predicted by the animal studies in the present series of drugs, possibly because blood pressure was not commonly measured in the animals under test, or alternatively because of the quadrupedal posture of animals in contrast to the orthograde posture of man. A number of more rarely reported effects are listed in Table 2. Certain of these side effects are subjective and are only made known to the observer by verbal reporting of the patient.

The data presented were also examined to determine how well animal and human data correlated for each individual drug. Thus each time a toxic effect in an animal study was matched by an analogous adverse reaction in man it was scored as a positive correlation. For example, if both animals and man vomited on the drug then that would be one correlation; if in addition they both showed bone marrow depression then that would be two correlations. The results of this analysis are shown in Table 3. Of the drugs having zero correlation, 10 were possibly accounted for by poor or inadequate data. Most (29) of the drugs showed either one or two correlations and one drug showed five; the latter was an analgesic and the correlations were vomiting, respiratory depression, sedation, drug dependence and salivation sweating. In only three instances was a clear negative correlation observed. A psychotropic agent and an analgesic were associated with excessive salivation in animals but with dry mouth in man, and a bronchodilator drug caused a rise in serum potassium in the dog but a fall in man.

It can be said with certainty that correlations between animal toxicity and adverse side effects in man do exist and that they are considerably more frequent than discrepancies. As a very approximate estimate, for any individual drug, up to 25% of the toxic effects observed in animal studies might be expected to occur as adverse reactions in man. It is also possible to say that there are some toxic effects in animals which are much more likely to occur also in man than others which are commonly seen in animals but rarely in man.

Predictive reliability of animal data

In retrospect, it is a relatively simple matter to determine the correlation between animal and human studies, but prospectively it is difficult to know which particular toxic effects are likely

Table 2. More rarely reported toxic and adverse effects of drugs in animals and man

Reaction	Animal	Human
Anorexia and failure to thrive	8	1
Splenic enlargement	5	0
Incontinence	4	0
Ptosis	4	0
Visual disturbances	1	2
Malignant tumours	3	0
Thymic defects	3	0
Lacrimation	3	0
Weight gain	2	1
Dependence	2	1
Hypotonus	1	0
Extrapyramidal	1	2
Neuromuscular	1	0
Local reaction	1	0
Hyperactivity	1	0
Weakness	1	0
Eye irritation	1	0
Piloerection	2	0
Gingival hyperplasia	1	0
Exophthalmos	1	0
Opisthotonos	1	0
Corneal changes	1	1
Paraesthesiae	0	2
Flushing	0	1
Metallic taste	0	1
Drug accumulation	0	1
Auditory defect	0	1
Euphoria	0	1
Discoloured urine	0	1
Itching	0	1
Hallucinations	0	1

Table 3. Individual drug correlations for toxic effects in animals and adverse effects in man

	Number of correlations					
	0	1	2	3	4	5
Number of drugs	13	17	12	3	2	1

to prove troublesome when it comes to giving the drug to man. At the present time it is not possible to say more than that some toxic effects (e.g. vomiting) carry a greater predictive capacity than others (e.g. salivation). Nevertheless, even the present rather crude analysis has shown that an assessment of predictive capacity is possible. It seems probable that extension of the number of drugs to 200 or more, together with more sophisticated classification and analysis, might yield relationships between animal toxicity and adverse effects in man that would greatly increase the predictive power of animal experiments.